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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/735,296	01/14/2000	Shu-Hsia Chen	6923-084	7224

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EXAMINER
CHEN, LIPING

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/735,296	Applicant(s) CHEN ET AL.	
	Examiner Liping Chen	Art Unit 1632	

-- The MAILING DATE of this communication appears on th cover sheet with the correspondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13,15,17,19 and 26-37* is/are pending in the application.

4a) Of the above claim(s) *27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13,15,17,19,26 and 28-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7 & 12* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Restriction/Election

Applicant's election with traverse of Group I, claims 13, 15, 17, 19 and 26-37, which is directed to a method for treating cancer comprising administering to a subject an effective amount of a first compound which is a nucleic acid molecule encoding activator of cytokine receptors, and a second compound which is 4-1BB ligand or derivative, in Paper No. 5, is acknowledged. The traversal is on the ground(s) that claim 13 is a proper generic claim and that groups I-IV are more properly characterized as species of a single generic invention. This is not found persuasive because Groups I-IV are directed to different combination of therapy: nucleic acid molecule encoding an activator of cytokine receptor + 4-1BB ligand, nucleic acid molecule encoding an activator of cytokine receptor + nucleic acid molecule encoding 4-1BB ligand, activator of cytokine receptor + 4-1BB ligand, and an activator of cytokine receptor + nucleic acid molecule encoding 4-1BB ligand, respectively. Search for a nucleic acid molecule encoding an activator of cytokine receptor does not require search for an activator of cytokine receptor, and vise versa; search for 4-1BB ligand does not require search for nucleic acid encoding 4-1BB ligand, and vice versa. Thus, the requirement is still deemed proper and is therefore made FINAL. Therefore, only Group I is examined in this office action.

Claims 13, 15, 17, 19, and 26, 28-37 are pending and are under current consideration only for nucleic acid encoding IL-12 or derivatives and 4-1BB ligand or derivatives. Claim 27 is not examined in this office action as it directed to a non-elected species IL-15 and IL-18.

Priority

This application is filed on 01/14/2000.

Priority claimed to provisional application 60/115,992, filed 01/15/1999.

Specification

The disclosure is objected to because of the following informalities:

Page 3, line 17, states "OX-40 (or CD134) expression is a member of". It is suggested this be written to state "OX-40 (or CD134) is a member of".

Page 3, line 27, states "Expression of 4-1BB s restricted to". It is suggested this be written to state "Expression of 4-1BB is restricted to".

The Description of the Figures for Fig. 5 is objected because it states "or combination ADV/IL-12 + anti-4-1BBL received a s.c. injection". This is not supported by the specification and Fig. 5, which only support ADV/IL-12 + ADV/4-1BBL treatment.

The Description of the Figures for Fig. 5 is objected because it states "only the results of the ADV/IL-12 + ADV/4-1BBL group reached statistical significance

compared to naïve controls (P=0.007, Fischer's exact test)". It is unclear this statistical significance is refer to animals injected with JC parental cells or animals injected with MCA26 parental cells. According to Fig. 5, the percentage of tumor formation is dramatically different between these two groups.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26, 28-37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 26 is directed to a method of treating cancer comprising administering to a subject in need an effective amount nucleic acid molecule comprising a nucleotide sequence encoding IL-12 and a second compound is 4-1BB ligand, a fragment, analog or derivative; Claim 28 is directed to a similar method of claim 26, but includes IL-12 fragment, derivative or analog; claims 29-37 are further directed to different embodiments as the following: claims 29 and 30 are directed to the nucleotide sequence encoding IL-12 or a its variant is contained in an expression

vector and regulated by a promoter; claim 31-33 are directed the nucleic acid molecule is contained in a viral vector; claim 34 is directed to human IL-12, claim 35 and 36 are directed to the subject as non-human mammal (claim 35) or a human (claim 36), claim 37 are directed to specific cancers including pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, lung cancer or hepatic cancer.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d at 1116. In the instant case, while a written description for a nucleic acid sequence encoding IL-12 (specification, page 12, line 28 to page 16, line 14) and 4-1BBL polypeptide (specification, page 29, line 7-20) is generally understood, there is no written description regarding the chemical structure of a fragment, derivative, or analog of IL-12 or 4-1BBL that has the activity of the respective full length one. Therefore, with the exception of full length of IL-12 and 4-1BBL, the skilled artisan cannot envision the detailed chemical structure of any fragment, derivative or analog of IL-12 or 4-1BB that possesses the function that is required for the purpose of treatment. The specification provides methods for identifying a fragment,

derivative or analog of IL-12 or 4-1BBL (specification, page 14, line 29 to page 15, line 6), therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method used. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of identifying it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *Pfaff v. Wells Electronics, Inc.*, 48 USPQ2d 1641, 1646 (1998).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence. In the instant case, only IL-12 and 4-1BBL meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 13, 15, 17, 19, 26 and 28-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling increasing survival rate of subject with solid tumors by intratumoral injection of Adv.mIL-12 in combination with 4-1BBL, does not reasonably provide enablement for increasing survival rate of a subject with other types of tumors or prevention or treatment of any cancer in a patient in need. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims

Claim 13 is directed to a method of treating or preventing cancer in a subject comprising administering to the subject a therapeutically effective amount of a compound that activated one or more cytokine receptor and a compound that activates one or more co-stimulator molecule expressed on activated immune cells; claim 15 is directed the method of claim 13, wherein at least one of the cytokine receptors is the IL-12 receptor; claims 17 and 19 are directed to the co-stimulatory molecules of claim 13 and 15, respectively, is 4-1BB; claim 26 is directed to a method of treating cancer comprising administering to a subject in need an effective amount nucleic acid molecule comprising a nucleotide sequence encoding IL-12 and a second compound is 4-1BB ligand, a fragment, analog or derivative; Claim 28 is directed to a similar method of claim 26, but includes IL-12 fragment, derivative or analog; claims 29-37 are further directed to different embodiments as the following: claims 29 and 30 are directed to the nucleotide sequence encoding IL-12 or a its

variant is contained in an expression vector and regulated by a promoter; claim 31-33 are directed the nucleic acid molecule is contained in a viral vector; claim 34 is directed to human IL-12, claim 35 and 36 are directed to the subject as non-human mammal (claim 35) or a human (claim 36), claim 37 are directed to specific cancers including pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, lung cancer or hepatic cancer.

The specification provides working examples to show an increased survival rate of BALB/c immunocompetent mice intrahepatically implanted with MCA26 tumor cell (Fig. 3), or mice bearing JC breast carcinoma (Fig. 4), after intratumorally injecting Adv.mIL-12 (1.6-3.2 x10^8 pfu) in combination with Adv.m4-1BBL (specification, page 38, line 9-29, and page 42, line 4-24). There is no evidence that injecting Adv.mIL-12 in combination with Adv.m4-1BBL or 4-1BBL will reduce any other types of tumors such as leukemia by system delivery. Moreover, the claims are directed to the use of a fragment, derivative or analog of IL-12 and 4-1BBL (pertaining to instant claims 26, 28-37), there is no teaching regarding chemical structure of any fragment, derivative or analog of IL-12 or 4-1BBl that has the function required for the treatment. There is no evidence that any claimed fragment, derivative or analog of IL-12 and 4-1BBL will increase survival rate of mice implanted with any tumors. With regard to cancer, it is well know in the art that cancer is a result of the accumulation of multiple abnormalities and a result of complex multistep process (Cooper, Oncogenes, Jones and Bartlett

Publishers, 1990, page 4, last parag.). Many tumor oncogenes (Cooper, page 76, Table 5.1, page 89, Table 6.1 and page 112, table 8.1) and tumor suppressor genes (Cooper, page 132-135) have been recognized to be related with certain types of carcinomas, and environmental exposure related with cancer formation has also been recognized (Feigelson, et al. J. Cell. Biochem. 25S:15-22, 1996, Abstract). There is no evidence that administering to a subject Adv.mIL-12 in combination with Adv.m4-1BBL or 4-1BBL will result in a treatment effect for cancers of different causes. Although the specification demonstrates intratumorally injecting Adv.mIL-12 in combination with Adv.m4-1BBL can increase survival rate of mice receiving the treatment, it is not equivalent to treating a cancer by reversing the pathological process. It is noticed that the specification does not provide data regarding the tumor volume changes for the mice receiving different treatment, therefore, it is not clear if an increased survival rate of mice receiving treatment is associated with a decreased tumor volume or other changes. Further, the specification only provides teaching for intratumoral injection of Adv.mLI-12 + Adv.m4-1BBL (specification, page 31, line 1-4), there is no guidance regarding different administration routes to achieve effective amount of transgene at any target site that is not reachable by direct injection, or to tumors, such as leukemia, that can not receive direct injection. With regard to gene therapy, the problems of the lack of efficient delivery systems, lack of sustained expression and host immune reactions has been well recognized in the art (Verma, Nature, 389:239-242, 1997,

page 239, col. 1). Rozenberg et al. (S.T.P. Pharma Sciences 11:21-30, 2001) teach that the choice of gene delivery vector is a key factor for the success of gene therapy application (Rozenberg, Abstract). The requirements for a vector to have successful gene delivery include ability to produce high titer vector particles, ability for efficient transgene expression for the desired duration, and low immunogenicity of the vector (Rozenberg, page 21, left col. sec. parag.). Although, the specification demonstrated intratumoral injection of Adv.mLI-12 + Adv.m4-1BBL lead to effective results for mice with implanted tumors, there is no evidence that different delivery route such as system delivery will result in effective amount of transgene expression at any target site. With regard to prevention of tumor metastases, the specification provides working example by challenging mice with JC or MCA26 tumor cells on left and right flanks implanted subcutaneously (specification, page 42, line 27-36). The results show that only JC tumor growing is inhibited in mice receiving treatment, and only the Adv.mLI-12 + Adv.m4-1BBL group reaches statistical significance comparing to controls (Fig. 5). There is no inhibition of tumor formation for mice implanted with MCA26 tumor cells in each treatment group comparing with the control group (Fig. 5). These data suggest different tumor has different response to administered Adv.mLI-12 + Adv.m4-1BBL. Further, these data are not correlated with prevention of tumor formation (pertaining to instant claims 13, 15, 17 and 19). The limitation of preventing tumor formation requires administration of the claimed formulations prior to the development of the

tumors. However, there is no guidance in the specification for determining the appropriate time prior to the development of tumors to begin the therapy or for identifying patients at risk for developing any tumors.

Therefore, in view of the results obtained from the working examples, the inconsistent response of different implanted tumor to administered Adv.mIL-12 + Adv.m4-1BBL, the lack of evidence that a fragment, derivative or analog of IL-12 and 4-1BBL will increase survival rate of any subject bearing with any tumor, the lack of evidence that using Adv.mIL-12 in combination with Adv.m4-1BBL will increase survival rate of a subject with tumors other than solid tumor by different route of transgene or peptide delivery, lack of evidence that using Adv.mLI-12 and Adv.m4-1BBL can prevent or treat cancers with different causes, based upon the nature of the invention, the state of the prior art, the complicity in tumor development and causes, the unpredictability in gene therapy, the claimed invention would have required one skilled in the art to engage in an undue amount of experimentation without a predictable degree of success to achieve any specific and the breath of the invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at

> the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 13, 15, 17, 19, 26, and 28-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Caruso et al. (PNAS 93:11302-11306, 1996) taken with Melero et al. (Eur J Immunol 28:1116-1121, 1998) and Vinay et al. (Semin Immunol. 10:481-489, 1998).

Claim 13 is directed to a method of treating or preventing cancer in a subject comprising administering to the subject a therapeutically effective amount of a compound that activated one or more cytokine receptor and a compound that activates one or more co-stimulator molecule expressed on activated immune cells; claim 15 is directed the method of claim 13, wherein at least one of the cytokine receptors is the IL-12 receptor; claims 17 and 19 are directed to the co-stimulatory molecules of claim 13 and 15, respectively, is 4-1BB; claim 26 is directed to a method of treating cancer comprising administering to a subject in need an effective amount nucleic acid molecule comprising a nucleotide sequence encoding IL-12 and a second compound is 4-1BB ligand, a fragment, analog or derivative; Claim 28 is directed to a similar method of claim 26, but includes IL-12 fragment, derivative or analog; claims 29-37 are further directed to different embodiments as the following: claims 29 and 30 are directed to the nucleotide sequence encoding IL-12 or a its variant is contained in an expression vector and regulated by a promoter; claim 31-33 are directed the nucleic acid molecule is contained in a viral vector; claim 34 is directed to human IL-12, claim 35 and 36 are directed to the subject as non-human

mammal (claim 35) or a human (claim 36), claim 37 are directed to specific cancers including pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, lung cancer or hepatic cancer.

Caruso et al. teach introtumoral administration of adenovirus expressing murine (m)IL-12 gene, ADV/mIL-12, into hepatic metastasis model mice of colon carcinoma prepared by intrahepatic implantation of 5 x 10^4 MCA-26 cells at the tip of the left lateral liver lobe of 8- to 12-week-old syngeneic BALB/mice (Caruso, page 11303, left col. first full parag. and page 11304, left col.), which results in a decreased tumor volume for the mice injected with ADV/mIL-12 (Caruso, page 11304, Fig. 4). Caruso et al. further demonstrate the antitumor functionality of ADV/mIL-12 is through induction of IFN-γ production (Caruso, page 11304, left col. and Fig. 3). Although Caruso et al. state the severe toxicity of using IL-12 alone for cancer treatment (Caruso, page 11305, right col. top parag.), Caruso et al. conclude that local expression of IL-12 may be an attractive treatment strategy for metastatic colon carcinoma (Caruso, Abstract). However, Caruso et al. does not teach to using IL-12 with 4-1BBL, or using 4-1BBL for reducing tumor volume.

Melero et al. teach using retroviral vector expressing 4-1BBL on P815 mastocytoma and AG104A sarcoma (Melero, page 1116, right col. last parag.) augments the immune response mediated by $CD8^+$ CTL and results in an associated specific tumor cells lyses (Melero, page 1118, Fig. 2). Melero et al. cures the deficiency of Caruso in that it teaches using 4-1BBL to amplify an antitumor

immune response. However, Melero et al. does not teach to use 4-1BBL with IL-12 for antitumor therapy, nor the mechanisms of 4-1BBL for increasing antitumor immune response.

Vinay et al. teach the 4-1BB signaling in co-stimulating the activated T cells by soluble 4-1BBL (Vinay, page 482, Fig. 1), which leads IFN-γ secretion in both murine and human (Vinay, page 481, right col. top parag.) and influence on various effector functions (Vinay, page 482, Fig. 1). Vinay et al. cures the deficiency of Melero in that it teaches the effect of 4-1BBL is through increasing the secretion of IFN-γ.

One of skill in the art of tumor cytockine therapy would be motivated to combine the teachings of Caruso et al. with the teaching of Melero et al. in view of the teachings of Vinay et al. because Caruso et al. teach antitumor functionality of ADV/mIL-12, which is through induction of IFN-γ secretion and the severe toxicity of using IL-12 alone for cancer treatment; Melero et al. teach amplifying the immune response mediated by $CD8^+$ CTL using 4-1BBL; Vinay et al. bridge the teaching of Caruso et al. and Melero et al. by teaching that the 4-1BB signaling in co-stimulating the activated T cells by soluble 4-1BBL is through induction of IFN-γ secretion. Since both functionality of IL-12 and 4-1BBL are related with induction of IFN-γ secretion, and both IL-12 and 4-1BBL have been demonstrated having reducing tumor functionalities, it would have been prima facie obvious at the time the invention was made to combine the teaching of Caruso et al. with the teaching

of Melero et al. to use both IL-12 and 4-1BBL for reducing tumor volume with decreased toxicity caused by using IL-12 alone and with reasonable expectation of success.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Liping Chen, whose telephone number is (703) 305-4842. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time). Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to Dianiece Jacobs, Patent Analyst, at (703) 305-3550. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-8724.

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